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Adaptive tracking with antagonistic pleiotropy results in seemingly neutral molecular evolution

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Supplementary Discussion

Our adaptive tracking model differs from another fluctuating selection model known as the quasi-neutral model[65,66] in that the fitness effect of an environment-dependent beneficial mutation averaged over many generations is negative in the former but nearly zero in the latter; as a result, they have distinct predictions (**Extended Data Fig. 8**). Similarly, our model differs from the fluctuating positive selection model in which an environment-dependent beneficial mutation's fitness effect over many generations is positive (**Extended Data Fig. 8**). Only the model of adaptive tracking with antagonistic pleiotropy produces both low α and low Ω that are generally consistent with observations. Further, our model differs from the recently proposed adaptive reversion model[67] in that temporarily beneficial mutations tend not to be fixed in our model but are fixed and then reversed and fixed again in the latter model. Because reverse mutations are improbable except in very large populations, our model is expected to be more widely applicable than the adaptive reversion model.

In our model, adaptive tracking can be driven by a *de novo* mutation if the mutation happens to be born in the environment where it is advantageous or a standing genetic variant if its favored environment arrives sometime after its birth but before its loss. Although we did not explicitly consider in our simulation, adaptive tracking may also be driven by genetic variants stably maintained by balancing selection[47]. Note that, while we have focused on explaining seemingly neutral patterns of molecular evolution, the adaptive tracking model can also generate patterns of adaptive molecular evolution under certain parameters (e.g., very small M, very large L, or very large F_{ben}), as shown in our simulations (**Fig. 2**, **Extended Data Fig. 3**).

In nature, environmental changes occur at all time scales, so the adaptive tracking model is in principle applicable to almost all species. However, environmental changes at very short time scales relative to the generation time of the species concerned may not trigger its adaptive tracking, because of the little chance for allele frequencies to respond to such brief environmental changes. Further analyses are needed to explore adaptive tracking under environmental changes of various time scales. Additionally, under the adaptive tracking model, an environmental change can result in many deleterious mutations segregating at non-trivial frequencies in the population, potentially generating a high genetic load. The level and consequence of this load await future studies.

One mechanism allowing rapid organismal responses to environmental changes is phenotypic plasticity[43]. One wonders why adaptive tracking instead of adaptive plasticity is observed in the response of yeast to changing media[40] and that of fruit flies to changing seasons[46,47]. In fact, phenotypic plasticity is common, but recent transcriptomic studies discovered that plasticity is mostly maladaptive instead of adaptive[70-72]. Just as mutations show antagonistic pleiotropy, it may be difficult to evolve plasticity that is beneficial across diverse new environments. Because environmental changes occur at all time scales, it will be interesting to explore whether adaptive plasticity and adaptive tracking deal with environmental changes at different time scales.

Note: All references cited here are also cited in the main text and are listed there.